DETAILED ACTION

Status of Claims

Claims 110 and 112 have been cancelled in an amendment filed 25 September 2007. As a result, Claims 107, 111 and 113-119 are pending and examined herein on the merits for patentability. No claim is allowed at this time.

Withdrawn Objection

The objection to claims 110 and 118, as well as 112 and 119, as being duplicates of one another is hereby withdrawn by the examiner in light the cancellation of claims 110 and 112.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 107, 111 and 113-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shenoy et al.

Applicant claims:

Claim 107 is drawn to a solid formulation comprising 35-45 wt.% of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 10-86 wt.% diluent (i.e. mannitol), 2-20 wt.% binder (i.e. croscarmellose sodium), 2-20 wt.% disintegrant (i.e. povidone), and 1-10 wt.% lubricant (i.e. magnesium stearate), wherein the formulation does not comprise a surfactant or a flow enhancer.

Claim 111 is drawn to a solid formulation comprising 10-16 wt.% 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 65-80 wt.% mannitol, 5-10 wt.% croscarmellose sodium, 4-8 wt.% povidone and 1-2 wt.% magnesium stearate.

Claim 113 is drawn to the formulation of Claim 107, wherein the formulation does not comprise a surfactant or flow enhancer.

Claims 114-116 are drawn to the bulk density of the formulation.

Claim 117 is drawn to the particle size of the solid formulation of Claim 107.

Claim 118 is drawn to a solid formulation comprising 40 wt.% 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 47.5 wt.% mannitol, 6 wt.% croscarmellose sodium, 5 wt.% povidone and 1.5 wt.% magnesium stearate.

Claim 119 is drawn to a solid formulation comprising 15.2 wt.% 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 72.7 wt.% mannitol, 6 wt.% croscarmellose sodium, 5.1 wt.% povidone and 1 wt.% magnesium stearate.

Determination of the scope and content of the prior art

(MPEP 2141.01)

With respect to Claim 111, Shenoy et al. teach a formulation comprising 0.01-***10*** wt.% ionizable substituted indolinone, 10-***80*** wt.% diluent, 0-***5*** wt.% binder, ***4***-10 wt.% disintegrant, and ***1***-1.5 wt.% lubricant (pages 92 and 93, Table: "All formulation components") (***emphasis added***).

With respect to Claims 107, 111 and 113-119, Shenoy et al. teach a formulation comprising 15-75 wt.% ionizable substituted indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer").

Shenoy et al. further teach that 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide is a suitable ionizable substituted indolinone (page 39, compound 80; and pages 158-159, Example 80). Shenoy et al. also teach that the ionizable substituted indolinone contemplated for use are pharmaceutically acceptable salts which do not abrogate the biological activity and properties of the compound (page 60, lines 1-6), wherein the ionizable substituted indolinone is reacted with a molar equivalent of a base solution or an acid solution, such as malic acid (page 65, lines 1-4; page 76, lines 1-3).

Shenoy et al. also teach suitable pharmaceutically acceptable diluents include mannitol (page 73, lines 14-15); suitable pharmaceutically acceptable binders include polyvinylpyrrolidone (i.e. povidone) (page 73, lines 17-18); suitable pharmaceutically acceptable disintegrants include croscarmellose (page 73, lines 19-21); suitable pharmaceutically acceptable lubricants include magnesium stearate (page 73, lines 26-27).

With respect to Claim 113, Shenoy et al. teach that the broadest range of surfactants and flow enhancers encompasses 0 wt.% (pages 92 and 93, Table: "All formulation components"; and page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer").

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Although Shenoy et al. teach 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide as a suitable ionizable substituted indolinone, and the acid solution comprising malic acid, Shenoy et al. do not explicitly teach the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide. However, it is well-known in the art at the time of the instant invention to employ pharmaceutically acceptable salts of compounds in pharmaceutical formulations in order to enhance the solubility of the compound, thus providing greater solubility. Shenoy et al. teach that salts tend to be more soluble in aqueous or other protonic solvents than are corresponding free base forms (page 87, lines 8-12).

With respect to claims 114-117 of the instant application, absent a showing to the contrary, since the instantly claimed formulations are obvious over Shenoy et al., the prior art compositions would inherently possess physicochemical properties (i.e., bulk density and particle sizes) that are identical to those claimed in Claims 114-117. As a result, Shenoy et al. anticipate said claims.

As a practical matter, the USPTO is not equipped with the scientific laboratory instrumentation and facilities necessary for the manufacture of the myriad of claimed products set forth before it and then obtain requisite prior art products so as to conduct side-by-side analytical comparisons of the physicochemical properties inherently associated therewith. See *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). The "discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." See *Atlas Powder Co. v. Ireco Inc.*, 51 USPQ 2d 1943, 1947 (Fed. Cir. 1999). Therefore, merely claiming a new use, new function or unknown property, which is inherently present in the prior art, does not necessarily make the claim patentable. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); and MPEP § 2112. Furthermore "products of identical chemical composition can not have mutually exclusive properties," since a chemical composition and its properties are inseparable. See *In re Spada*, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990); and MPEP § 2112. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. See MPEP § 2112.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to use the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide in the formulations of Shenoy et al. because Shenoy et al. reasonably teach 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide as a suitable ionizable substituted indolinone and that salts tend to be more soluble in aqueous or other protonic solvents than are corresponding free base forms.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's Remarks filed 25 September 2007 have been fully considered but they are not persuasive. Applicants argue on pages 4-5 that it would not have been obvious to modify the teachings of Shenoy et al. to select the malate salt of the ionizable substituted indolinone, nor would it have been obvious to select the specific narrow ranges of components in order to produce a composition having improved bulk density and processing properties. Applicants further argue that the comparative

examples within the instant specification (paragraphs [0469], [0470], [478] and [0479] of the application publication US 2004/0229930) show that the properties of the formulation such as bulk density are not inherent in the Shenoy et al. disclosure.

The examiner respectfully disagrees. With respect to the selection of the malate salt of the ionizable substituted indolinones, Shenoy et al. clearly teach salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms (pg. 87, ll. 11-12; and pg. 82, ll. 24-25). Shenoy et al. further teach that the ionizable substituted indolinones contemplated for use in their invention are pharmaceutically acceptable salts (pg. 60, ll. 1-2), and the indolinone is solubilized by combining it with a molar equivalent of a base or an acid solution (pg. 64), such as malic acid (pg. 65, ll. 1-4; pg. 76, ll. 1-3; pg. 79, l. 30 through pg. 80, l. 1; pg. 87, ll. 8-11; and claim 11). Therefore, Shenoy et al. clearly teaches the desire to use the pharmaceutically acceptable salt of the ionizable substituted indolinones, wherein malic acid is one of the preferred acid solutions for solubilizing said indolinones.

With respect to the concentration of the components, Shenoy et al. teach a set of ranges that is suitable for their invention, wherein the ionizable substituted indolinone is present from 5-90%, preferably 1-80%, and most preferably 15-75%, as acknowledged by Applicants (pg. 96, 2nd table). Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to use the ionizable substituted indolinone at 35 to 45 wt.% as instantly claimed.

Applicants argue that a composition comprising 75 wt.% of the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic

acid (2-diethylamino-ethyl)-amide results in a composition having undesirable sticking problems in the manufacturing process, whereas compositions with only 40 wt.% or 15.2 wt.% display no sticking problems.

However, Applicants have not performed a side by side comparison with the closest prior art composition. Shenoy et al. teaches specific examples of compositions wherein the ionizable substituted indolinone is present at concentrations of 5, 20, 25 and 28 wt.% (Examples 5 and 6). Therefore, the argument that the comparative examples show that the properties of the formulations such as bulk density are not inherent in the Shenoy et al. disclosure is not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616